II. REMARKS

The Office Action indicates that the application does not contain an abstract of the disclosure. The undersigned represents that the abstract on page 37 of the application was submitted to the patent office along with the rest of the application papers on the filing date of December 14, 2000. A copy of the stamped return postcard acknowledging receipt of the abstract page by the PTO is attached herewith as evidence. However, for the completeness of the Examiner's file, the undersigned is providing herewith another copy of the abstract page.

The Office also indicates that copies of the 85 references listed in the form PTO-1449 were not found and requested that Applicants produce these documents. The undersigned submits that the IDS mailed to the patent office on June 28, 2001, indicated on page 2 that a copy of each of the items listed on the form PTO-1449 was supplied, and again, the stamped return postcard, a copy of which is attached herewith, confirms receipt of these items at the patent office on July 2, 2001. As a courtesy to the Office, Applicants are sending a second set of these 85 documents under separate cover. The Examiner is requested to initial the form 1449 and return a copy of the initialed form to applicants.

Status of the claims

Claims 1-9 and 17-19 have been examined and are rejected on various grounds. These rejections are addressed in the appropriate sections below.

By virtue of this amendment, claims 2, 3, 4, 5 and 17 are canceled, claims 1, 6, 7, 8, 9, 18 and 19 are amended, and claims 20 to 25 are added. Applicants reserve the right to prosecute any canceled subject matter in a continuation application. Claims 1, 6-9, 18-25 will be pending upon entry of this amendment.

Claim 20 is supported in the specification on page 15 at lines 25-26. Claims 21-23 are supported in the specification on page 16 at lines 5-8 and 28-33. Claims 24 and 25 find support in the specification on page 18 at lines 30-33.

Claim 1 is amended to incorporate claim 17 and part of claim 4, which claims are now canceled. Claims 6, 7 and 19 are amended to correct the dependency upon the cancellation of certain claims from which it previously depended. Claims 8 and 9 are amended to delete the typographical error, "one of". The amendments to claim 8 find support on page 16 at lines 34-35 and page 14 at lines 10-16. Claim 18 is amended to correct the dependency and to link CH2 and CH3 domains. The amendments to the claims should overcome the objections based on incorrect or improper dependency. The amendments to the claims are supported by the

specification and claims and no new matter has been introduced. Entry of these amendments and reexamination and reconsideration of the claims, as amended, are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."** For the Examiner's convenience, a clean copy of the pending claims, as amended, is provided in an appendix attached herewith.

Rejections under 35 U.S.C §112, second paragraph

Claims 8-9 and 18 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. Each of claims 8 and 9 unnecessarily recites "one of claim" when only one claim is listed. In claim 18, the Office alleges that it is unclear whether the extracellular ligand binding portion of human tumor necrosis factor is linked alternatively to each of these domains, the hinge, the CH2 domain, and the CH3 domain of human IgG1, or if the ligand binding portion was linked to the Fc portion of human IgG1 which contains the hinge, CH2 and CH3 domains.

With regard to claims 8 and 9, the amendment to these claims to delete the typographical error "one of" overcome this rejection.

With regard to claim 18, applicants submit that the claim is not indefinite since it clearly recites that the ligand binding portion of human TNF is linked to the hinge, CH2 domain and CH3 domain of the IgG1; the claim does not recite these domains using the alternative, "or". It is clear to one reading the specification on page 14 at lines 6-7 which states that "...the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule [underline added]", that the extracellular ligand binding portion is linked to the constant regions of IgG1 containing in order, the hinge, CH2 and CH3 domains, and not linked alternatively and separately to each of these domains. Otherwise, the "or" in that sentence would not make sense. At present, claim 18 has been amended to recite the hinge, CH2 and CH3 domains of human IgG1, as supported in the specification on page 14 at lines 6-7, to further clarify that distinction.

Applicants believe that all the rejections on the grounds of indefiniteness have been adequately addressed and that the above amendments to the claims overcome the rejections. Therefore, it is respectfully requested that these rejections under §112, second paragraph, be withdrawn.

Rejections under 35 U.S.C §112, first paragraph

Claims 1-8, 17 and 19 are rejected under 35 U.S.C §112, first paragraph on various grounds including that the specification fails to provide any guidance as to how to make and use any LFA-1 antagonist and any TNF-α antagonist.

The Examiner has acknowledged that the specification is enabled for and applicants are in possession of a method of treating rheumatoid arthritis comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF-α receptor - IgG Fc fusion protein.

These rejections are overcome in part by amendment and traversed in part.

Claim 1 has been amended to recite rheumatoid arthritis and anti-CD11a antibody. In addition, claim 8 has been amended to specify the portions of the TNF-α receptor and of the immunoglobulin that are fused to make the immunoadhesin. Amended claim 8 now recites that the immunoadhesin is a fusion of at least a "TNF-α binding portion of a TNF-α receptor and an immunoglobulin constant domain sequence".

Applicants disagree with the Office that the specification is not enabled for any LFA-1 antagonist and any TNF-α antagonist useful for the treatment of LFA-1 and TNF-α mediated disorders and that applicants disclosed only anti-CD11a antibody and TNF-α-receptor-IgG Fc fusion protein. Many of these antagonists are known in the art. Pages 4 and 15 of the specification disclose LFA-1 antagonists including a list of anti-CD11a antibodies and anti-CD18 antibodies which antibodies are well characterized in the literature as referenced and are available commercially or through the ATCC. However, in the interest of expediting prosecution, applicants have amended claim 1 to recite anti-CD11a antibody instead of LFA-1 antagonist.

Similarly, the specification on pages 3 and 16-17 discloses numerous examples of TNF-α antagonists including Enbrel™, type I and type II TNFR immunoadhesins and several anti-TNF antibodies that are in use in the clinic. For example, the anti-TNF-α chimeric antibody, Remicade®, is commercially available and is an approved for the treatment of rheumatoid arthritis (RA). For the D2E7 antibody (Humira™; Cambridge Antibody Technology and Abbott labs), Phase III clinical trials in patients with RA have been completed, the reports of which indicated reduction in RA signs and symptoms and inhibition of joint destruction in patients treated with Humira. RA patients treated with Enbrel, Remicade or Humira were also administered or continued to receive methotrexate during treatment with these drugs. Other

TNF-α antagonists disclosed include soluble TNF-α binding proteins such as the naturally occurring extracellular portion of the type I TNFR, TBP-1 which is a TNF binding protein, and compounds which reduce the levels of TNF-α in tissues.

In addition, the specification on page 17, line 7 through page 22 provides guidance on route of administration, dosages and compositions of the LFA-1 and TNF-α antagonists for administration to patients for the treatment of RA as well as other disorders associated with LFA-1 and TNF-α taught in the subsequent pages.

In view of the preceding remarks, applicants submit that the specification fully provides guidance on how to make LFA-1 and TNF-α antagonists and how to use these molecules to treat rheumatoid arthritis and other disorders mediated by LFA-1 and TNF-α. In particular, applicants submit that the specification has provided sufficient description of a representative number of species of TNF-α antagonists with known function in vitro as well as in vivo to support the genus of TNF-α antagonists as recited in amended claim 1. Therefore, it is respectfully requested that the rejections under 35 U.S.C §112, first paragraph, be withdrawn.

Rejections under 35 U.S.C §102(e)

Claims 1-6 and 17 have been rejected under 35 U.S.C. §102 (e) as allegedly anticipated by U.S. Patent No. 6,037,454 ('454 patent), as evidenced by Genentech: News Release of Thursday, June 21, 2001. It is the Office's belief that the '454 patent (col. 4, lines 35-67; col. 5, lines 1-37 in particular) teaches humanized anti-CD11a antibodies that can be administered to a mammal with an immunosuppressive agent such as anti-TNF-α antibodies to treat a LFA-1 mediated disorder such as rheumatoid arthritis.

Applicants traverse this rejection on the basis of the following remarks. Patent '454 does not teach a method of treating RA comprising administering to the mammal, an anti-CD11a antibody and a TNF-α antagonist. Patent '454 at col. 4, line 66 through col. 5, line 37 as referenced by the Office, discloses immunosuppressive agents including anti-TNF-α antibodies. However, the term "immunosuppressive agent" in that discussion was used in the context of graft rejection and organ transplant. The term "immunosuppressive agent" as used therein was specifically defined as "substances that act to suppress or mask the immune system of the host into which the graft is being transplanted [underline added]." The column discusses substances that suppress self antigen or mask MHC antigens, as well OKT3 antibodies. In the discussion in col. 5 at lines 29-32, it is stated that the preferred immunosuppressive agent will depend on many factors including "the type of transplantation being performed". Column 5 does not specifically

teach administering anti-TNF-α antibodies for treating RA. Turning to the question of the inherency of the anti-CD11a antibody as a non-T-cell depleting antibody, the discussion is moot in view of the lack of anticipation of claim 1.

In view of the preceding, patent '454 cannot anticipate pending claims 1 and 6. It is respectfully requested that the rejection under 35 U.S.C. 102 (e) be withdrawn.

Rejections under 35 U.S.C §103

Claims 7-9 and 18-19 have been rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over U.S. Patent No. 6,037,454 taken with U.S. Patent No. 6,306,820 or in view of the ENBREL disclosed in the specification on page 16, line 5 and page 17, lines 4-5.

This rejection is traversed on the following grounds. U.S. Patent No. 6,037,454 is not available as prior art under 35 U.S.C. §103(a) as §103(c) applies. The present application has a priority date of December 14, 1999, which is before the issue date of patent '454; therefore, patent '454 can qualify as prior art only under §102(e). Both patent '454 (see cover page) and the present application (recorded on reel/frame 011737/0739) are assigned to Genentech, Inc. Patent '820 fails to teach or suggest any anti-LFA-1 antagonist let alone anti-CD11a antibody in combination therapy with a TNF-α antagonist in a method of treating RA. The known description of ENBREL alone does not render accomplish the method of the claimed invention. Therefore, the claims cannot be obvious.

Applicants request that this §103 rejection be withdrawn.

III. CONCLUSION

Applicants submit that the above discussion is fully responsive to all grounds of rejection set forth in the Office Action. In view of the comments above, Applicants respectfully request that all outstanding rejections be withdrawn, and that the pending claims, as amended, be allowed. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 07-0630 (Ref. Docket No. P1795R1). However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,
GENENTECH, INC.

Date: January 16, 2003

By: Lee Tan

Lee K. Tan, Ph.D. (Ms.)
Reg. No. 39,447
Telephone: (650)225-4462

document #122124

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. (Amended) A method of treating rheumatoid arthritis [an LFA-1 or a TNF-α mediated disorder], comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody [LFA-1 antagonist] and a TNF-α antagonist.

6. (Twice amended) The method of claim 1 [17], wherein the anti-CD11a antibody is a non T-cell depleting antibody.

7. (Twice amended) The method of claim 1 [any one of claims 1-6 and 17], wherein the TNF-α antagonist is an immunoadhesin.

8. (Amended) The method of [one of] claim 7 wherein the immunoadhesin is a fusion of at least a TNF-α binding portion of a TNF-α receptor [binding protein] and [a portion of] an immunoglobulin constant domain sequence.

9. (Amended) The method of [one of] claim 8, wherein the immunoadhesin [TNF-α binding protein] is a TNF-α receptor - IgG Fc fusion protein.

18. (Amended) The method of claim 9 [10], wherein the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge region, CH2 [domain,] and CH3 domains [domain] of human IgG1.

19. (Amended) The method of claim 1 or claim 18 [4], further comprising administering to the mammal an effective amount of methotrexate.

APPENDIX OF PENDING CLAIMS AS AMENDED ON JANUARY 16, 2003

1. (Amended) A method of treating rheumatoid arthritis, comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF-α antagonist.

6. (Twice amended) The method of claim 1, wherein the anti-CD11a antibody is a non T-cell depleting antibody.

7. (Twice amended) The method of claim 1, wherein the TNF-α antagonist is an immunoadhesin.

8. (Amended) The method of claim 7, wherein the immunoadhesin is a fusion of at least a TNF-α binding portion of a TNF-α receptor and an immunoglobulin constant domain sequence.

9. (Amended) The method of claim 8, wherein the immunoadhesin is a TNF-α receptor - IgG Fc fusion protein.

18. (Amended) The method of claim 9, wherein the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge region, CH2 and CH3 domains of human IgG1.

19. (Amended) The method of claim 1 or claim 18, further comprising administering to the mammal an effective amount of methotrexate.

20. (New) The method of claim 1 or claim 9, wherein the anti-CD11a antibody is a humanized antibody.

21. (New) The method of claim 1, wherein the TNF-α antagonist is an anti-TNF-α antibody.

22. (New) The method of claim 21, wherein the anti-TNF-α antibody is a chimeric monoclonal antibody.

23. (New) The method of claim 21, wherein the anti-TNF-α antibody is a human or humanized monoclonal antibody.

24. (New) The method of claim 18, wherein the anti-CD11a antibody and fusion protein are administered sequentially.

25. (New) The method of claim 18, wherein the anti-CD11a antibody and fusion protein are administered concurrently.

In re Application of: Wyne P. Lee et al.
Serial No.: 09/738,540
Filed On: 14 December 2000
Mailed On: June 28, 2001

Docket No.: P1795R1
By: Lee K. Tan
Reg. No.: 39,447

7/11/01

The following has been received in the U.S. Patent Office on the date stamped:

X Information Disclosure Statement
X Form 1449 with 85 References
X Certificate of Mailing
X A copy of the PCT Search Report

In re Application of: Lee et al.
Serial No.: To Be Assigned
Filed On: 14 December 2000
Mailed On: 14 December 2000

Docket No.: P1795R1
By: Lee K. Tan, Ph.D.
Reg. No.: 39,447

The following has been received in the U.S. Patent Office on the date stamped:

- X U.S. Patent Application Transmittal (dup) (Non-Provisional)
- ___ Filing Fee ($)
  - 35 Pages of Specification
  - 1 Pages of Claims
  - 1 Page(s) of Abstract
  - 5 Sheets of Drawings X Formal __ Informal
- X Declaration/Power of Atty(unsigned)
- ___ Extension of Time Request ()
- ___ Assignment w/ Recordation Form and Fee ($40.00)
- ___ Information Disclosure Statement w/ PTO-1449 and __ References
- ___ Sequence Listing w/ Diskette and Certificate re: Sequence Listing
- X Certificate of Express Mailing Express Mail Label No.: EL 747359719 US
- ___ Other: